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ORIGINAL ARTICLE

⁶⁸Ga-citrate PET/CT in tuberculosis: a pilot study

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ABSTRACT

BACKGROUND: Tuberculosis remains an important cause of morbidity and mortality worldwide, the diagnosis, staging and treatment response evaluation of which remains sub-optimal. We evaluated PET/CT imaging with a novel tracer, ⁶⁸Ga-citrate, in this setting.

METHODS: Thirteen patients with tuberculosis underwent PET/CT imaging with ⁶⁸Ga-citrate. Tuberculosis was diagnosed with bacteriological or histopathology studies (N=8) or based on a combination of clinical data, biochemistry and imaging (N=5). PET images were analyzed qualitatively and semi-quantitatively and compared to CT findings.

RESULTS: All 13 patients demonstrated abnormal tracer accumulation in the lungs or extra-pulmonary or both. ⁶⁸Ga-citrate accumulated in every lung lesion noted on CT in six cases (46%). In seven cases (54%) some of the lung lesions noted on CT were not ⁶⁸Ga-citrate avid, which is suggestive of non-active tuberculous lesions. Ten patients (77%) demonstrated extrapulmonary involvement, which included various lymph node groups, skeletal lesions, pleural-, splenic- and gastrointestinal tract involvement. Detection of extra-pulmonary involvement was higher on PET compared to CT (more lesions detected) in eight cases (80%).

CONCLUSIONS: ⁶⁸Ga-citrate PET accumulates in both pulmonary and extra-pulmonary tuberculous lesions and may provide a way of distinguishing active from inactive lesions for treatment response evaluation. ⁶⁸Ga-citrate PET may be superior to CT in the detection of extrapulmonary involvement.

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KEY WORDS: Positron-emission tomography - Infection - Diagnostic imaging - Tuberculosis.

Tuberculosis (TB) is a major contributor to mortality and morbidity in developing countries and continues to present physicians with diagnostic challenges. In the South African setting, these problems are compounded by the frequent coinfection with HIV, subsequent reactivation associated disease and the relatively high prevalence of drug-resistant TB.¹⁻³

Imaging with PET/CT provides clinicians with a non-invasive tool, which is capable of early detection, assessment of the extent of pulmonary and extrapulmonary involvement as well as treatment response evaluation. PET/CT imaging is potentially invaluable in the management of patients infected with mycobacterium TB.

The most frequently used PET tracer in this setting to date is ¹⁸F-FDG. However, several studies have demonstrated its limitations in distinguishing TB from malignant lesions.^{4, 5}

⁶⁷Gallium-citrate SPECT imaging has been widely used in the setting of immunosuppression with suspected lung involvement. Imaging with the PET tracer ⁶⁸Gallium-citrate should theoretically provide the same clinically useful information with the added advantages of PET/CT imaging. These include better resolution, improved logistics with shorter imaging time and less radiation exposure. In addition, this generator-produced tracer provides round-the clock, yearlong availability.^{6, 7} To the best of the authors' knowledge, ⁶⁸Ga-citrate has not yet been evaluated in this setting. Preliminary data demonstrate its usefulness in the setting of musculoskeletal infections.^{8, 9}

The aim of this pilot study was to describe ⁶⁸Ga-citrate PET/CT findings in patients with TB.

Materials and methods

Study population

Thirteen patients with a diagnosis of TB were included prospectively in this study following written informed consent. Approval to conduct this study was granted by the Ethics Committee of the University Hospital of Pretoria (Protocol no 93/2011).

Tuberculosis was diagnosed with bacteriological or histopathology studies (N.=8) or based on a combination of clinical data, biochemistry and imaging (N.=5).

Labeling protocol for ⁶⁸Ga-citrate

A SnO₂-based ⁶⁸Ge/⁶⁸Ga generator with a 1.85 GBq loading activity (iThemba LABS, Somerset West, South Africa) was used for radiolabeling.⁹ ⁶⁸Ga-citrate synthesis was performed manually in a straightforward, one-step-aseptic procedure, which was based on a combination of the protocols used by Kumar¹⁰ and Rizzello.¹¹ All routine quality control requirements were met.

Image acquisition

Study participants were imaged on a Siemens Biograph 40 PET/CT camera at 60 minutes following IV administration of 185 MBq of ⁶⁸Ga-citrate. Seven patients underwent additional delayed imaging at 120 minutes post-injection. Both oral and IV contrast was administered, except where a contraindication existed.

Image interpretation

PET studies were evaluated and reported by two experienced nuclear physicians and CT images were evaluated and reported by two experienced radiologists. Any disagreements were resolved by reaching consensus.

Qualitative analysis

Images were initially evaluated qualitatively. Any tracer accumulation outside of the normal biodistribution was considered abnormal and compared to the liver according to the following scale: 1/low=less intense than the liver, 2/moderate= equal to the liver, 3/high=more intense than the liver.¹²

Quantitative analysis

A region of interest was drawn manually around any abnormal tracer accumulation in such a way as to correspond

to the size of the lesion on CT. The maximum standardized uptake value (SUV_{max}) was recorded for each lesion. This value is obtained from the following calculation: SUV=radioactivity x patient weight/injected dose. We used the maximum SUV (SUV_{max}) in this study, which represents the pixel with the highest tracer uptake in the lesion. Where dual time point imaging was performed (N.=7), a second SUV_{max} was recorded. The 60 minute value was labeled SUV_{max1} and the 120 min image SUV_{max2}. The change in SUVmax was calculated as follows (and expressed as a percentage change up or down):

The difference between SUV_{max1} and SUV_{max2}/ SUV_{max1} x 100.

Statistical analysis

Descriptive statistics were used to report patient characteristics and procedural details. Summary statistics is presented as mean (SD, standard deviation) or as median (IQR, interquartile range) in case of non-normality of the data. Numbers or percentages are reported otherwise. Statistical analysis was performed with STATA version 10.

Results

Demographics

The study participants consisted of 5 males (38.5%) and 8 females (61.5%) with a median age of 40 years. Four patients (31%) were Caucasian and 9 (69%) were Black.

Clinical presentation

The most frequent clinical presentation (N.=10) was one or a combination of the following: a productive or non-productive, intermittent cough (hemoptysis rarely reported), dyspnea, chest pain and loss of weight. None of these patients reported a history of previous TB. Five patients (38.5%) had confirmed concomitant HIV infection and were presumed to have reactivation TB.

Procedural

The median injected dose of ⁶⁸Ga-citrate was 196 MBq (155-255MBq). The average radiochemical purity determined by ITLC was 98.9±0.94% which was confirmed by HPLC. The pH value of the product for injection was 4.0-4.5. All other requirements for QC were met. IV contrast was administered in ten patients (77%).

PET/CT findings

Images obtained at 60 minutes post-injection of (on average) 185 MBq of ⁶⁸Ga-citrate, resulted in good quality images. ⁶⁸Ga-citrate images demonstrated high vascular activity, as has been demonstrated before.¹¹ In addition, normal biodistribution demonstrated increased tracer accumulation in the salivary glands, liver, spleen and bone marrow.

Qualitative evaluation (relative to the liver intensity) demonstrated low ⁶⁸Ga-citrate uptake in 5 patients (38.5%) moderate to high uptake in 5 (38.5%) and high tracer accumulation in 3 (23%). Dual time point imaging demonstrated a decrease in SUV_{max} from 60 min to 120 min in five patients (71.43%) ranging from 2-34%, and an increase in two patients (28.57%) of 24% and 32%.

All 13 patients demonstrated abnormal tracer accumulation in the lungs or extrapulmonary or both. SUV_{max} values ranged from 1.19-8.69 with a median SUV_{max} of 3.71 (25th percentile=2.19; 75th percentile=4.95) (Table I).

⁶⁸Ga-citrate accumulated in every lung lesion noted on CT in six cases (46%). In the other seven cases (54%) some of the lung lesions noted on CT were not ⁶⁸Ga-citrate avid, which is suggestive of non-active tuberculous lesions (Figure 1).

Ten patients (77%) demonstrated extra-pulmonary involvement, which included the pleura (Figure 2), various lymphnode groups (Figure 3), skeletal lesions (Figure 4)

and involvement of various soft tissues, the spleen and gastrointestinal tract. Detection of extrapulmonary involvement was higher on PET compared to CT (more lesions detected) in 8 cases (80%). The remaining 2 cases (20%) demonstrated equal detection on both modalities and none of these patients demonstrated central nervous involvement on either study.

Figure 1.—A) A 57-year-old old HIV negative female presented with a mass in the left upper lobe (3.5x3 cm) on CXR. PCR demonstrated Mycobacterium tuberculosis complex, sensitive to INH and rifampicin. B) PET/CT images were acquired 60 minutes following IV injection of 166.5 MBq of ⁶⁸Ga-citrate. IV contrast was given. Moderately increased tracer uptake was noted in the LUL mass (SUV_{max}: 5.24). The abnormal tracer accumulation was noted in the left lower lobe (SUV_{max}: 2.55, SUV_{max2} 3.37, increase of 32%). Liver SUV_{max}: 3.59.

TABLE I.—Individual patient diagnostic details.

No	Lung lesion	Other areas of involvement	Diagnostic modality and detail	⁶⁸ Ga-uptake*
1	Right upper lobe nodule	None	Sputum	Low
2	Left upper lobe nodule	None	Combination clinical and imaging	Low
3	Left upper lobe mass	Cervical and mediastinal lymph nodes	PCR, sensitive to INR and rifampicin	Moderate
4	Right upper lobe nodules	Multiple lymph nodes, spleen, GIT	Liver biopsy: Large numbers of AFBs on Ziehl-Neelsen stain	Low
5	Right pleural effusion	Right hemithorax, mediastinal lymph nodes, skeletal, soft tissue	Pleural fluid analysis	High
6	Left lung nodule	None	Combination clinical and imaging	Moderate
7	Left lung changes	Mediastinal, axillary and inguinal lymph nodes	Sputum MCS	Moderate
8	Mediastinal lymph nodes	Skeletal, spleen, kidneys lymphnodes, soft tissue	Combination clinical and imaging	High
9	Right upper lobe changes	Mid-thoracic spine (T6-T8)	PCR, sensitive to INR and rifampicin	Low
10	Bilateral apical thick-walled cavitations	Skeletal, soft tissues, lymphnodes	Combination clinical and imaging	High
11	Left upper lobe cavities	Mediastinal lymphnodes	PCR, sensitive to INR and rifampicin	Moderate to high
12	Mediastinal mass	Widespread lymphnodes, spleen, mycotic aneurysm	Combination clinical and imaging	Low
13	Right lung apex	Lymphnodes (supraclavicular, porta hepatis)	AFB+ on aspirates	Moderate to high

*Low: less than the liver; Moderate: equal to liver; High: more than the liver.

Figure 2.—A 28-year-old man with a large right-sided pleural effusion and *Mycobacterium Tuberculosis* on pleural fluid analysis. Dual-time point imaging was performed at 60 minutes and 120 minutes following IV administration of 224.59 MBq of ^{68}Ga -citrate and IV contrast. Intense tracer accumulation was noted in the anterior chest wall and posterior thickened pleura on the right. (SUV_{max1} 7.42; SUV_{max2} 7.17; decrease of 3.4 %) Liver SUV_{max} 3.90.

Due to ethical considerations, every lesion detected on PET could not be biopsied and histologically verified. Based on similar results found with ^{67}Ga -citrate,¹³⁻¹⁶ it would be reasonable to suggest that areas of increased extrapulmonary tracer accumulation represent additional sites of tuberculous involvement. False positives may occur due to malignant lesions, however, none of the patients in this pilot study had any known soft tissue malignancy.

Suspected extra-pulmonary involvement consisted of the following: skeletal involvement of the sternum (N.=1), ribs (N.=2), vertebral bodies (N.=6), skull base (N.=2), pubic symphysis (N.=1), hip (N.=1), humerus (N.=1). Of

Figure 3.—Forty-year-old man with TB and HIV-co-infection demonstrating enlarged lymphnodes with necrotic centers and peripheral rim tracer accumulation, similar to what has been demonstrated with ^{18}F -FDG PET/CT. 232MBq (6.3 mCi) of ^{68}Ga -citrate was injected IV, up-take time 60 min, IV contrast given.

these lesions, the base of skull- and the humerus involvement was not detected on CT. Half of the vertebral body lesions were not seen on CT. Liver involvement was detected in 4 patients, of which 2 were not seen on CT and splenic involvement in 5 patients (detected on both modalities). Kidney involvement was suspected in 4 patients (two of which were not seen on CT) and gastrointestinal involvement in 1 patient, which was not visible on CT.

CT findings

The upper pulmonary lobes were the most frequently involved areas, followed by mediastinal- and other lymph

Figure 4.—A 44-year-old male with HIV and TB (Absolute CD4 196 x106/L) who presented with quadriparesis. CT demonstrates destruction of the vertebral bodies of C4/C5 and the intervertebral disc with intense tracer accumulation in this region. Dual-time point imaging was performed following IV injection of 257.5 MBq (6.96mCi) of ⁶⁸Ga-citrate and IV contrast. SUV_{max1} of 3.83 decreased by 2% to a SUV_{max2} of 3.75. (Liver SUV_{max}: 3.24).

phnode involvement as well as pleural involvement. Lung changes consisted of the following: nodules in one or both lungs (8 patients), diffuse infiltrates (4 patients), emphysema/bronchiectasis/atelectasis/consolidation (4 patients), cavitations (2 patients), ground glass opacities (1 patient) and tree-in-bud pattern (2 patients). Six patients demonstrated mediastinal lymphadenopathy; 5 demonstrated pleural involvement and 2 also had soft tissue masses.

Additional special investigations

All patients also had a chest radiograph prior to PET/CT imaging, which was abnormal in only 4 cases (31%).

Hyponatremia as a result of inappropriate ADH secretion has been reported in patients with pulmonary disease and more specifically, in TB.¹⁷ We have noticed the same trend; where recent sodium results were available (N.=8), 6 patients (75%) demonstrated low sodium values (rang-

ing from 127 to 134 mmol/L). The other two patients had values that were on the very low limit of normal.

Another frequent biochemistry abnormality is an abnormal full blood count (FBC), which in our study was present in all of the patients who had a recent FBC (N.=10). The most frequently observed abnormality was anemia (with hemoglobin values ranging from 7.4-13.7 g/dL) and the presence of pancytopenia in two patients. Albumin levels were low in all, ranging from 24-30 g/L. In the patients with confirmed HIV infection, CD4 and viral counts were not readily available.

Discussion

The importance of TB and its impact on mortality and morbidity is indisputable worldwide and even more so in countries with a high prevalence of HIV coinfection and increasing multi-drug resistance. Development of a non-invasive diagnostic tool capable of early and accurate detection, staging and follow-up evaluation of tuberculosis is therefore of the utmost importance in minimizing the devastating effects of TB.

The pathophysiology of TB is still incompletely understood, but involves both protective and immune-pathogenic mechanisms.¹⁸ Airborne tuberculosis bacilli reach the alveolar space where macrophages, local dendritic cells and epithelial cells that line the bronchi and alveoli rapidly take it up. Mycobacterium Tuberculosis then delays onset of the host's adaptive immune response for 2-3 weeks, presumably in order to establish a critical bacilli mass. This is probably achieved by interfering with the "homing" process. M TB persists in the infected host cells where it evades the host immune response by inhibiting the maturation of bacterial phagosomes, apoptosis, antigen processing and IFN- γ receptor-mediated signaling. Triggering of the host's protective immune response eventually leads to granuloma formation, which consists of centrally located M TB and macrophages and peripheral T-cells. Experimentation with a zebra fish model¹⁹ has demonstrated that granulomas are actually dynamic structures that host cells can move in and out of quickly. Uncontrolled local infection and inflammation finally results in caseous necrosis, which greatly promotes further bacterial growth and airborne spread of large numbers of bacilli.¹⁸

The acquired immunodeficiency syndrome epidemic has lead to a higher incidence of tuberculosis with changed disease patterns and increases in disseminated and extra-

pulmonary involvement. Extrapulmonary tuberculosis can occur with or without pulmonary involvement and may affect any organ. The most frequently reported affected sites include lymph nodes, the pleurae, musculoskeletal, gastrointestinal and genito-urinary tract involvement.²⁰ Despite recent advances; the diagnosis and assessment of extent of extrapulmonary involvement remains problematic. This is important when deciding on the correct treatment regimen, since it involves prolonged treatment and, in some cases, the addition of corticosteroids.

In our study, all of the patients with HIV coinfection had pulmonary and extra-pulmonary involvement. Despite neurological symptoms in three patients, no central nervous system involvement was demonstrated on ⁶⁸Ga-citrate PET/CT. This is consistent with the findings reported by Lin and Hsieh.²¹

Current diagnostic modalities include a variety of tests ranging from clinical evaluation, imaging and skin tests to advanced serological, immunological and histopathological analysis. Unfortunately, all of these suffer from various limitations in sensitivity and specificity and may only be useful in particular clinical situations. It seems that the gold standard remains bacteriological cultures for now, which is not always possible and causes a significant delay in reaching the diagnosis.^{22, 23}

PET/CT imaging provides a non-invasive diagnostic tool, which combines the high-resolution morphological CT information with the molecular disease information from PET in one whole body evaluation. While radiological features may remain unchanged during early treatment, evaluation with PET provides an early indication of response to treatment.

Several authors have now investigated the use of ¹⁸F-FDG PET/CT in settings with a high prevalence of granulomatous disease. ¹⁸F-FDG PET/CT is essentially based on the detection of increased glucose metabolism, which in TB is mainly due to increased macrophage and neutrophil activity.

Satheke *et al.* made the following contributions with regards to ¹⁸F-FDG PET/CT imaging in TB:

- ¹⁸F-FDG detects more TB lesions, especially extrapulmonary, when compared to CT;
- the number of lymph node bastions can be used to predict treatment response in patients with TB and HIV coinfection. Five bastions provide the cut-off between treatment responsive and non-responsive TB patients (sensitivity 88%, specificity 81%, NPV 93%);²⁴
- a higher SUV_{max} was also noted in the lymph nodes

of non-responders. A cut-off of 4.5 can be used to discriminate between responders and non-responders with a sensitivity of 95% and specificity of 85%;²⁴

— lymphnodes with central attenuation and peripheral enhancement were also associated with non-response to tuberculostatics.²⁵

Several authors have also demonstrated the value of ¹⁸F-FDG PET/CT in follow-up and treatment response evaluation of TB, especially with extrapulmonary involvement and where drug-resistance is prevalent.²⁶⁻²⁸

Soussan *et al.*²⁹ identified two different patterns of tuberculosis on FDG-PET; a pulmonary type with a more localized type of infection and a lymphatic pattern of involvement associated with a more intense, systemic infection.

Despite the above-mentioned advances made, several limitations remain, such as the inability to differentiate between malignant lesions and TB^{4, 30} and cyclotron dependency.

The uptake mechanism of Gallium is complex, incompletely understood and involves several direct as well as indirect mechanisms. Local inflammation and vasodilation results in increased tracer accumulation due to higher tracer delivery (indirect), while direct mechanisms are the result of Gallium's similarity to iron. Its accumulation in tuberculous lesions is believed to be the result of transcapillary exudation of transferrin-bound gallium and subsequent binding to leucocytes and bacteria. Gallium accumulation is therefore unaffected by the impaired cellular immunity found in patients with HIV.³¹

⁶⁷Ga-citrate has played an important role in the diagnosis and management of patients with TB and HIV as early as the 1970s. Sarkar *et al.*¹³ evaluated the use of ⁶⁷Ga-citrate imaging in eleven patients with suspected extrapulmonary involvement and found that it could correctly predict the absence or presence of active disease. They also suggested that ⁶⁷Ga-citrate should be routinely used in patients with suspected extrapulmonary involvement and that it would probably be valuable in the follow-up evaluation since scan findings correlated well with clinical improvement. Several other authors have evaluated the use of Gallium imaging in patients with immuno-suppression and lung diseases such as tuberculosis with similar conclusions reached.^{12, 14-16}

In summary, PET/CT imaging provides clinicians with a one-stop non-invasive tool for the assessment and response evaluation of active pulmonary, and especially extrapulmonary, TB. ⁶⁸Ga-citrate is an alternative genera-

tor-produced PET tracer, which could potentially be more cost-effective and may suffer from fewer limitations when compared to ¹⁸F-FDG. Larger trials with ⁶⁸Ga-citrate are needed to evaluate the value of dual-time point imaging in distinguishing tuberculosis from malignant lesions.

Conclusions

⁶⁸Ga-citrate PET accumulates in both pulmonary and extrapulmonary tuberculous lesions and may provide a way of distinguishing active from inactive lesions for treatment response evaluation. In addition, ⁶⁸Ga-citrate PET appears superior to CT in the detection of extra-pulmonary involvement.

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